

Paraquat — a Review of Safety in Agricultural and Horticultural Use

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- 1 Over the past 20 years plus that paraquat has been used throughout the world, it has enjoyed an excellent safety record when used normally and for its intended purpose.
- 2 Its safety record is explained by the following reasons: (i) inhalational exposure during normal use is not significant toxicologically; (ii) dermal exposure predominates during normal use; (iii) intact human skin provides a very good barrier against penetration by paraquat.
- 3 Its safety record has been confirmed by several field studies, which have assessed exposure and health of workers, who have used paraquat for short and longer periods of time. The unanimous conclusions of the studies is that exposure to paraquat does not result in any acute or chronic adverse health effects.
- 4 Minor and reversible injuries to the skin, eyes, nose and nails do occur and probably result from overexposure to the extremely irritant concentrated formulations. Most of these effects can be avoided using ordinary personal hygiene.
- 5 There have been a few anecdotal cases reported in the literature when dermal absorption of paraquat has genuinely occurred and led to serious health effects. In all cases prolonged exposure to concentrated paraquat solutions has been involved resulting in severe and extensive skin damage, with removal of the barrier and absorption of lethal amounts of the chemical.
- 6 Those cases involving exposure to concentrated paraquat solutions emphasise the need to handle such formulations, for example 'Gramoxone', with care and ensure that the spray solution is correctly made up—at a dilution of at least 1 part 'Gramoxone' to 40 parts water.

Introduction

Paraquat was first introduced as a broad spectrum contact herbicide in 1962. Since then, sales of the herbicide have expanded throughout the world, so that it is now used in over 130 countries. Several formulations are available, but the most common is 'Gramoxone', an aqueous concentrate containing 200 g paraquat ion per litre. Prior to application the concentrated formulation is diluted with water at least 40 times and very often 100 to 200 times to form a spray solution. The spray may be applied by hand-held or vehicle-mounted sprayers or by air.

Over the 20 years plus it has been sold, it is our experience that the normal use of paraquat has not led to serious health injury or fatality with workers using the product. Normal use does not necessarily equate with recommended use, since it may also involve minor and predictable deviations from recommended use. These deviations include blowing out blockages in nozzles, leaking sprayers, or spillages. Furthermore normal use does not always involve the use of protective clothing or equipment.

The purpose of this review is to examine the evidence for paraquat's safety in normal use and to explain the reason for it. It is not the aim of this paper, to review its abuse, with which toxicological incidents are usually associated and may be defined as a use of the chemical for which it was never intended, for example ingestion, injection or deliberate dermal application. However misuse of paraquat, which may be defined as use of the product associated with gross deviation from label recommendations, is addressed.

Exposure during normal use

Several exposure studies with paraquat have been carried out under actual field spraying conditions, using hand-held sprayers as well as tractor and aerial application. The exposure to covered and uncovered skin was determined by chemical analysis of patches placed on different body regions.¹ Inhalational exposure (including oral exposure) was established

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Table 1 Worker exposure to paraquat

Application method	Exposure to uncovered skin (mg h^{-1})	Exposure to covered and uncovered skin (mg h^{-1})	Inhalational* exposure (mg h^{-1})	Reference
Hand-held (Knapsack)	0–12	12–170	(0–5) $\times 10^{-3}$	Chester & Woollen ²
Vehicle-mounted	0.01–3.4	—	(0–2) $\times 10^{-3}$	Staiff <i>et al.</i> ³
	3.6–50.4	12–169	(0–70) $\times 10^{-3}$	Wojek <i>et al.</i> ⁴
Aerial-Flagger	0.1–2.4	—	(0–47) $\times 10^{-3}$	Chester & Ward ⁵
Pilot	0.05–0.26	—	(0–0.6) $\times 10^{-3}$	

* Assumes a lung ventilation of $1.8 \text{ m}^3 \text{ h}^{-1}$

using personal air sampling equipment and the air concentration of different particle sizes of paraquat was determined. The data from these studies are summarised in Table 1.

It is evident from these results that skin exposure represents by far the most significant route of absorption, since inhalation exposure is approximately three orders of magnitude less than skin exposure. Furthermore inhalational exposure of paraquat is toxicologically insignificant. The Time Weighted Average Threshold Limit Value (TLV) for paraquat is currently 0.1 mg m^{-3} (American Conference of Governmental Industrial Hygienist 1982/3)⁶ equivalent to 0.18 mg h^{-1} , which is much greater than the inhalational exposure measured during paraquat use. Also the TLV assumes inhalation of respirable particle ($1\text{--}7 \mu\text{m}$ mean diameter) only, whereas the figures quoted in Table 1 represent total inhalational exposure, including respirable and non-respirable droplets. It is worth noting that Chester & Ward⁵ reported that no respirable droplets of paraquat could be detected during aerial application.

This very low inhalational exposure is explained by the fact that paraquat is non-volatile and applied as a spray containing relatively large droplets which are downwardly directed. Application of very fine droplets, which could drift, is not recommended for paraquat use. The insignificance of inhalational exposure and the significance of dermal exposure during herbicide application has been confirmed in a recent study by the British Agrochemicals Association.⁷

Dermal absorption

Since the above data leads us to the conclusion that skin exposure is the important route of absorption to consider, understanding of the skin penetration of paraquat is necessary to evaluate its safety in use. Knowledge of dermal penetration of chemicals has

improved in recent years and several laboratory techniques to measure it are currently available.⁸

The ability of paraquat to penetrate skin has been studied in the laboratory using an *in vitro* technique with both animal and human skin.⁹ The technique involves insertion of a section of epidermis (from human or animal skin) between two glass diffusion chambers (see Figure 1). Human epidermis is obtained by immersing post-mortem samples of abdominal skin in water at 60°C for 40–45 s. Animal epidermal samples are prepared using a similar technique involving the use of chemical reagents. With the sample in place, between the chambers and supported on a metal grid, a solution of chemical is introduced into the 'Donor Chamber'.

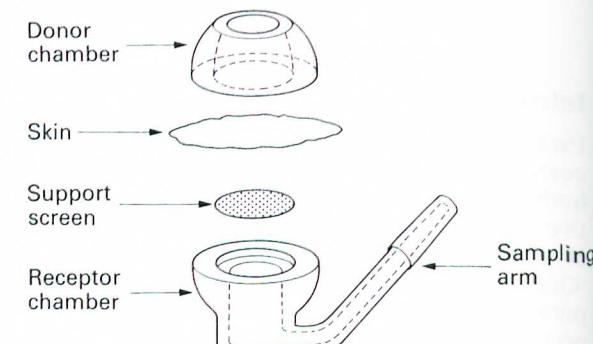


Figure 1 *In vitro* method for assessment of skin penetration by chemicals

The 'Receptor Chamber', containing water and/or suitable solvent is then sampled at different time intervals and the samples analysed for chemical content. The analysis provides information on the amount of chemical which has penetrated the epidermal section over a given period of time. By knowing

the surface area of contact, the rate of skin penetration, in terms of amount (μg) per unit area (cm^2) per unit time (h) can be calculated. The permeability constant (units of cm h^{-1}) can also be calculated and represents the rate of penetration divided by the concentration of chemical applied.

Using this technique it has been shown that intact human skin is a very good barrier to paraquat in solution, at concentrations equivalent to those used in sprays applied in practice. Furthermore, Walker *et al.*⁹ showed that the permeability of skin to paraquat is much less than the permeability of skin to many other chemicals. These data are summarised in Table 2 below.

Confirmation of these *in vitro* results, has been provided by Wester *et al.*¹⁰, who examined percutaneous penetration of paraquat using human subjects. The results of this human study, which also used a spray strength solution of the chemical, gave a similar rate of penetration to the *in vitro* model.

Walker *et al.*⁹ also showed that human skin is much less permeable to paraquat than the skin of several animals (Table 3). Thus by comparing the figures in the right-hand column we find for example that rat skin is $40 \times$ and rabbit skin is $130 \times$ more

permeable to paraquat than human skin. From this it is clear that the dermal LD₅₀ carried out on animals (usually rat and rabbit) gives a large overestimate of the potential hazard of paraquat to man by this route.

In summary the importance of the dermal route of absorption during normal use together with the excellence of the skin as a barrier help to explain why paraquat is safe to use. This explanation has been reinforced by the results of field surveys examining the health of workers exposed to paraquat.

Field studies with spray operators

Swan¹¹ described two of the earliest studies demonstrating the safety in use of paraquat. The two studies were conducted in Malaysia, where exposure tends to be heavy and the use of paraquat is intense. Clothing worn consisted of shirt or singlet, long trousers (tucked into the socks) and variety of footwear ranging from open sandals to leather boots. Each study involved exposure of 6 workers to the herbicide over a 12-week period, (6 working days per week) and the native workers (2 Chinese, 2 Malaysian and 2 Indian) were medically assessed before, during and after each spraying trial.

Table 2 Permeability of human skin to chemicals⁹

Chemicals	Vehicle	Permeability constant ($\text{cm h}^{-1} \times 10^5$)	Lag time (h)
Toluene	Ethanol/water 1:1	2100	0.06
HCN	Water	1000	0.05
Cyanide ion	Water	35	1.5
Hexachlorophene	pH 8.8 Aqueous	220	22
Water	Water	100	0.4
Progesterone	Water	150	2.5
Cortisone	Water	1	220
Paraquat	Water	0.75	24

Table 3 Permeability of animal and human skin to paraquat

Species	Water permeability ($\text{Perm Const. } \text{cm h}^{-1} \times 10^{-5}$)	Paraquat permeability ($\text{Perm. Const. } \text{cm h}^{-1} \times 10^{-5}$)	Permeability increase relative to man
Man	93	0.75	—
Rat	103	27.2*	40
Hairless rat	130	35.3*	50
Nude rat	152	35.5*	50
Mouse	144	97.2*	135
Hairless mouse	351	1065*	1460
Rabbit	255*	79.9*	130
Guinea pig	442*	19.6*	270

* Significantly different from human

None of the workers showed any serious adverse health effects which could be attributed to paraquat exposure. In particular no worker exhibited any lung abnormality detectable by chest radiography.

Approximately half the number of workers had some irritation of the eyes or skin at some time during the 12-week exposure. With the exception of two cases of scrotal dermatitis, produced by exceptionally prolonged contact with the chemical, all these effects were mild and cleared rapidly within 24 to 48 h. Only one man of the twelve complained of epistaxis. He had been spraying on a steep hillside downwind of the other workers. The nasal mucosa was very congested, but returned to normal after a few days.

Urine levels of paraquat were measured throughout the study. Most of the levels fell below $0.1 \mu\text{g ml}^{-1}$ of paraquat ion with a maximum recorded value of $0.37 \mu\text{g ml}^{-1}$. The author compared these levels with urinary levels from patients, who had swallowed paraquat accidentally or with suicidal intent. In two cases which survived one (Leading article BMJ¹³) had a urine concentration of $44 \mu\text{g ml}^{-1}$ in the first 24 h falling to $5 \mu\text{g ml}^{-1}$ after 48 h. In the other¹² the urine level was measured at $148 \mu\text{g ml}^{-1}$ some hours after ingestion. This patient, who was thought to have swallowed 2 g of paraquat ion, also survived.

Swan concluded that 'ordinary care in personal hygiene is sufficient to prevent any hazard from surface injury or from systemic absorption'.

In another study on the exposure of spray operators to paraquat in Ireland, Hogarty¹⁴ points out that no fatalities, from spraying in accordance with recommended practice, have been reported. This is in sharp contrast with cases involving ingestion of the chemical.

Hogarty showed that the number of spray droplets produced, which were less than $16 \mu\text{m}$ diameter was very small during application and that the number of respirable droplets was about 0.001% of the total number of droplets. On measuring air and urine concentrations of paraquat, Hogarty could not detect any airborne paraquat and urine samples were negative for paraquat. Medical tests indicated that spraying paraquat had had no effect on the health of the three workers involved and that no paraquat was likely to have been inhaled or ingested during the trial.

Hogarty concluded that 'there is little or no risk attached to the use of paraquat dichloride as an agricultural herbicide, provided recommended methods of application are adhered to'.

This conclusion was largely supported by Hearn and Keir¹⁵ who also demonstrated the development of local nail effects in 53 out of 296 workers on Trinidad sugar estates, but found no evidence of effects from systemic absorption. The dilutions of 'Gramoxone' were from 1:100 to 1:200 (i.e. from 0.2

to 0.1 per cent paraquat ion in the final spray solution).

More recently a survey of 36 paraquat dichloride formulation workers in England and Malaysia by Howard¹⁶ also failed to show any systemic effects from the dermal absorption of paraquat, although the incidence of local reactions indicated that the workers had been exposed to the compound in the formulating process. It is worth noting that this group included persons who had been exposed to paraquat for long periods of time (up to 12 years of workplace exposure) and there was no evidence of chronic skin problems nor of any effects on lungs or other organs.

Howard¹⁷ also produced a detailed review of paraquat worker exposure in normal usage. He concludes that the available evidence supports the conception that systemic poisoning from recommended agricultural use does not occur.

However, on rare occasions during the last 20 years there have been incidents, reported in the literature,¹⁸⁻²³ in which extensive skin damage has led to increased dermal absorption and death from systematic paraquat poisoning. Without exception, these cases arose from gross misuse of the product. It must be stressed that contact with high concentrations of paraquat over a prolonged period, so as to cause extensive skin damage and removal of the barrier, is a prerequisite for the absorption of a lethal amount of paraquat. In two of the references cited (Jaros *et al.*¹⁸ and Levin *et al.*¹⁹), workers had been using relatively high concentration sprays (4% and 2.8% paraquat ion respectively, which is specifically against the manufacturer's recommendations. The concentrated sprays produced severe and extensive skin damage in both cases, and death resulted from dermal absorption of paraquat.

The effect of prolonged contact of concentrated paraquat solution on the skin was also demonstrated by Athanaselis *et al.*²⁰ Once again the concentration of paraquat spray solution used (probably in excess of 1-2% paraquat ion) was far higher than the maximum recommended by the manufacturer (0.5% w/v paraquat ion).²⁴

The case described by Waight²¹ resulted from breakage of a bottle containing concentrated paraquat solution carried in the patient's pocket and subsequent prolonged contact of this on the skin. In the other two cases,^{22,23} undiluted 'Gramoxone' was used to kill body lice by applying liberally to the scrotal area—clearly a form of abuse.

In the above cases, there is little doubt that paraquat poisoning took place by dermal penetration. In many cases however the route of absorption is in doubt, mainly because a patient has denied swallowing the product. In such cases, for example that described by Newhouse *et al.*,²⁵ a diagnosis of dermal poisoning is speculated. However careful analysis of these cases, can reveal the presence of symptoms, which

are consistent with ingestion despite denial by the patient. In the case described by Newhouse *et al.*, the patient exhibited nausea and vomiting, which are far more likely to have occurred from the ingestion of paraquat than from dermal contact.

Safety of paraquat—long-term use

It has often been reported in the literature that ingestion of paraquat may lead to accumulation of the chemical into the lung with the consequent result of lung damage. Due to its lung damaging potential, concern has arisen as to whether long-term exposure to paraquat will also result in lung accumulation and damage.

The accumulation of paraquat into the lung is both time and energy dependent and will obey saturation kinetics.²⁶ This means that as the concentration of paraquat in the plasma falls, the rate of uptake into the lung will also fall. At the same time as paraquat is taken up into the lung, it is also being removed from the lung. A plasma concentration will eventually be reached, when the rate at which paraquat enters the lung will be equal to the rate at which it is removed and at this concentration no lung accumulation will occur. For animal models, e.g. the rat, this concentration can be calculated to be between 0.2 and 0.5 $\mu\text{g ml}^{-1}$.²⁷ Since laboratory studies have shown that human lung behaves similarly towards paraquat as rat lung,²⁸ it is reasonable to conclude that continuous plasma levels of between 0.2 and 0.5 $\mu\text{g ml}^{-1}$ of paraquat ion will not lead to lung accumulation and damage in man.

Further evidence of a plasma concentration threshold, below which lung accumulation and damage will not occur is available from animal studies. Rats exposed to an aerosol of paraquat (particle size $< 3 \mu\text{m}$) containing 0.1 μg paraquat ion/litre for 6 hours per day, five days per week for three weeks do not develop lung damage.²⁹ Furthermore, although

lung levels rose during the first few exposures, they eventually reached a stable level of $1 \mu\text{g g}^{-1}$ of lung tissue. Rats fed on a diet containing 150 mg kg^{-1} of paraquat did not develop lung damage as defined under light microscopy and the lung levels did not exceed $0.5 \mu\text{g g}^{-1}$ of lung.³⁰

In occupational use of paraquat, although plasma concentrations have not been directly measured, urine concentrations have been reported in two studies. Swan¹¹ found that urine concentrations usually contained less than $0.1 \mu\text{g ml}^{-1}$ of paraquat ion with a maximum recorded value of $0.37 \mu\text{g ml}^{-1}$. Chester & Woollen² found urine levels were usually below $0.05 \mu\text{g ml}^{-1}$ paraquat ion (maximum of $0.76 \mu\text{g ml}^{-1}$).

It is well recognised that paraquat is excreted unchanged in the urine. With normal renal function the rate of excretion is greater than the rate of clearance by glomerular filtration (Davies).³¹ Therefore it is reasonable to assume that the concentration of paraquat in urine will greatly exceed the plasma from repeated exposure, and that plasma paraquat concentrations in workers are likely to be much lower than the urine concentrations measured and probably non-detectable ($< 0.01 \mu\text{g/ml}$). Under these circumstances lung accumulation and resultant lung damage will not occur.

It was not surprising, therefore, that when Howard *et al.*³² evaluated the health of 27 agricultural workers, who had a long history of paraquat exposure in Malaysia (average 5.3 years exposure), no difference was observed between the health of these workers and the health of the two non-exposed control groups (factory and general estate workers). In particular there was no difference in lung functions, including transfer factor, and no difference in blood biochemistry for hepatic and renal function. Howard concluded that the long-term exposure under Malaysian conditions did not result in any serious health effects.

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The Epidemiology and Prevention of Paraquat Poisoning

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- 1 In the UK there was an increase in the annual number of deaths associated with paraquat poisoning between 1966 and 1975. Since that time there has been little change in numbers.
- 2 High mortality is associated commonly with suicidal intent. Serious accidental poisoning from paraquat has never been frequent in the UK and there have been no deaths reported in children since 1977.
- 3 The National Poisons Information Service has monitored in detail all reports of paraquat poisoning since 1980. Of the 1074 cases recorded there were 209 deaths. In recent years serious poisoning has been more commonly associated with ingestion of concentrated products by males. Local exposure to paraquat has not resulted in systemic poisoning.
- 4 International data for paraquat poisoning is incomplete and difficult to compare. There is a scarcity of morbidity data at both international and national levels. Information obtained from Poison Control Centres indicates that paraquat poisoning occurs in many countries but detailed comparisons are hindered by lack of standardised methods of recording.
- 5 Various measures to prevent paraquat poisoning have been introduced. Their effectiveness has not been studied in detail. Some support is provided by the low incidence of serious accidental paraquat poisoning in the UK, but because of the suicidal nature of paraquat poisoning it is unlikely that current preventative measures will influence the number of deaths occurring each year.
- 6 Preventative measures against paraquat poisoning should be tailored to national needs, based on and assessed by epidemiological studies.

Introduction

The preceding papers have stressed both the importance of paraquat to agriculture, and its safety when correctly used. Paraquat is, nevertheless, toxic to man and this toxicity has been the subject of a great deal of attention in the scientific and 'lay' press. The first cases of paraquat poisoning occurred in 1964, in Ireland and New Zealand (Bullivant, 1966) and by 1970 some 600 fatalities had been reported in the world literature (IPCS, 1984). In spite of the interest, it remains a difficult task to describe the mortality and morbidity associated with paraquat poisoning in different countries in strict epidemiological terms. Such a description requires appropriate and comparable mortality and morbidity statistics. A recent review found that 'because of the different requirements or practices for notification or reporting of cases of poisoning in the many countries in which paraquat is used, the magnitude of the problem is difficult, if not impossible, to determine' (IPCS, 1984). We concur with this view after reviewing the information available from Poison Control Centres, routine sources of mortality and morbidity data and from scientific reports. The information available

from these sources is presented and the measures aimed at preventing paraquat poisoning reviewed.

Sources of information

1. Hospital based surveys

The Home Accident Surveillance Scheme (HASS) records standardised data from a sample of twenty Accident and Emergency (A&E) departments in England and Wales on all types of home accidents (Consumer Safety Unit). A request was made for the number of admissions due to home accidents with weedkillers occurring during the period October 1982 to October 1984. In addition the results of an epidemiological study of acute poisoning cases attending twenty one A&E departments in England and Wales were examined (Murray, Francis & Thompson 1986).

2. Poison Control Centre reports

These reports include the results of a five-year surveillance of paraquat poisoning undertaken by the National Poisons Information Service (NPIS) and the

manufacturer (ICI plc) since 1980. Details of the methods used have been previously published (Hart & Bramley, 1983; Whitehead, Volans & Hart, 1984). In addition the results of a survey amongst European Poison Control Centres of the incidence of paraquat poisoning, undertaken by the secretary of the European Association of Poison Control Centres (EAPCC) (Wickström, 1984) have been examined together with other information from Poison Control Centres given directly to the authors.

3. Mortality statistics

Statistics for England and Wales published in the *Pharmaceutical Journal* for 1966–1973 and by the Office of Population Censuses and Surveys (OPCS) for 1974–1984 have been used. Data was not published in 1981 in England and Wales due to industrial action.

For Scotland, statistics were obtained from the Annual Report of the Registrar General from 1967 to 1984.

4. Other sources

Information from the Agrochemical Poisoning Appraisal Panel (APAP) which is administered by the Health and Safety Executive to investigate reports of occupationally related pesticide poisonings together with information published in the scientific press has been analysed.

Morbidity from paraquat poisoning

1. Hospital based surveys

From October 1982 to October 1984, over 287,000 home accidents were reported to HASS. Of the 39 which were due to weedkillers only seven could be identified as containing paraquat. Four of these involved children under 2 years of age, but only one was admitted into hospital. Limitations in the HASS reporting system, for example fatalities not being included and trade names not always being recorded, may mean that this number of cases is an underestimate.

A preliminary report showed that over a period of one year 22195 cases of acute poisoning attended A&E departments in England and Wales. Only 14 cases of exposure to paraquat were recorded (Murray *et al.*, 1986). The number of admissions to the hospitals in the study represent approximately 12.5% of all admissions in England and Wales. The total number of exposures due to paraquat may therefore be estimated at 112 but final figures are expected to be higher (J. Francis, personal communication).

A retrospective study of cases of self-poisoning presenting at the United Norwich Hospitals during the

five-year period 1978–1982 found twelve admissions due to paraquat (Adams, 1986).

An important source of morbidity data, the Hospital-In-Patient enquiry (HIPE), fails to document admissions due to paraquat. This is because the International Classification of Diseases (ICD) used for coding the cause of admission has no specific code for paraquat. Any information would be contained in a general category, such as admission due to toxic effects of 'other substances chiefly non-medicinal as to source'.

Outside the UK we found no published national morbidity information concerning paraquat. A national study conducted by the Environmental Protection Agency in the United States concerning hospitalised pesticide poisonings failed to document any cases due to paraquat, even though 2954 admissions due to pesticides were reported in 1974 (G.R.A. and I., 1981).

We therefore concur with a recent report that there are no published national morbidity statistics for pesticides (Vale & Buckley 1986) and that this is particularly true for paraquat. For this reason Poison Control Centres have been identified as potential sources of 'morbidity data' (Brzezinski 1976; Volans & Wiseman, 1986).

2. Poison Control Centre (PCC) reports

(a) *United Kingdom – National Poisons Information Service (NPIS)*. Over the period 1980 to 1985, more than 1000 cases of exposure to paraquat were reported to the NPIS (Table 1). 70% (760) of all cases involved ingestion. Other reported routes of exposure were inhalation (9.8%), skin contact (9.3%), eye contact (2.3%) and injection (0.7%). Of these routes only ingestion and injection led to symptoms of systemic poisoning, though one case of skin contact resulted in a positive urine test.

Of all the cases of ingestion 13% of patients were under five-years-old, 2% were aged between 5 and 12 years, and 85% were older than 12 years. Outcome of the incident was confirmed in 81% of cases (67% survival) by the attending physician, generally about four to five months after the incident. It was not possible to obtain complete follow-up because of difficulties in tracing patients who were not admitted into hospital.

The proportion of survivors having symptoms was estimated for 1984, when 74% of adults had symptoms whereas in the under 5 age group only one child (8.3%) had.

The Agrochemical Poisoning Appraisal Panel recorded three occupationally related paraquat poisonings in 1982.

Thus paraquat poisoning does not seem to represent a problem: to children, by skin and eye contact, inhalation, and through occupational contact.

Table 1 Paraquat cases notified to the NPIS over the years 1980–1985

Year	Total number of cases	Number of cases of ingestion	Age and outcome of ingestion cases									Number of deaths by ingestion	Total number of deaths
			< 5 yrs			5–12 yrs			> 12 yrs				
			S	D	NK	S	D	NK	S	D	NK		
1980	152	121	11	—	3	—	—	1	54	37	15	37	37
1981	169	127	4	—	2	1	—	—	57	45	18	45	47
1982	223	154	16	—	5	—	—	1	78	38	16	38	41
1983	198	143	15	—	8	—	—	5	64	33	18	33	33
1984	189	132	12	—	9	3	—	1	58	32	17	32	32
1985*	143	83	9	—	8	1	—	1	26	19	19	19	19
Total	1074	760	67	—	35	5	—	9	337	204	103	204	209

S: Survival D: Death NK: Not known

* Provisional figures

Table 2 Cases of paraquat poisoning reported internationally

Country	Cases (fatalities in brackets)					Source
	1980	1981	1982	1983	1984	
UK	152 (37)	169 (47)	223 (41)	198 (33)	189 (32)	NPIS
England & Wales	(24)	NK	(31)	(36)	(31)	OPCS
Scotland	(6)	(12)	(9)	(5)	(9)	Registrar General
Denmark			(3 over 3 years)			Copenhagen PCC
France	90	106	83	NK	NK	Wickström*
	27 (20)	—	—	—	—	Freelan 1983
Germany (West)	25	49	65	85	80	Wickström*
Greece	NK (13)	NK (4)	59 (9)	54 (14)	53 (7)	Athens PCC
Eire	29	39	19	NK	NK	Dublin PCC
Netherlands			(8 from 1978–1983)			Wickström*
Czechoslovakia			(2 to 3 per annum)			Wickström*
Norway	6 (3)	7 (0)	12 (10)	NK	NK	Wickström*
Poland	NK	NK	7	NK	NK	Wickström*
Spain	1 (0)	2 (0)	0	0	0	Wickström*
Sweden	10 (1)	8 (2)	8 (1)	6 (3)	3 (2)	Stockholm PCC
Switzerland						Zurich PCC
Israel	NK	(4)	(2)	(0)	(0)	Haifa PCC
Australia	NK	NK	11	8	10	Canberra PCC
Fiji	—	—	49 (30)	59 (33)	—	Groundar 1984
Japan	NK	NK	NK	NK	(1300)	Naito 1986
USA					153 (1)	AAPCC 1984

* Personal communication

(b) *Other countries* Cases of paraquat poisoning recorded over the period 1980–1984 are shown in Table 2. This shows that there are differences in the extent of paraquat poisoning with relatively little occurring in Sweden, Norway, Czechoslovakia and West Germany. However the comparability of these figures is not known because of the different methods of recording and following-up cases and nature of the services provided by the different countries. For example poison control centres in the United States accept enquiries from members of the public, unlike centres in the United Kingdom.

Mortality from paraquat poisoning

1. National mortality statistics

Figure 1 shows the number of fatalities recorded per year in England and Wales, Scotland and Eire for the period 1965–1984. In England and Wales, the first fatalities due to paraquat poisoning were recorded in 1966. Over the ten-year period to 1975, fatalities increased from 1 to 43 cases per annum with a rapid increase occurring between 1971 and 1975. Numbers since 1975—although fluctuating—have not changed significantly, 31 were recorded in 1984.

2. Other countries

No national published mortality statistics listing paraquat were found. Data on mortality is published by the World Health Organisation, however only a broad categorisation of poisoning based on ICD codes is given, paraquat therefore is not listed. The same limitations were found with vital statistics available from individual countries.

Additional information regarding fatalities due to paraquat may be obtained from Poison Control Centres.

3. Poison Control Centre reports

a. United Kingdom—National Poisons Information Service.

Of the 1074 cases of paraquat exposure reported to the NPIS, 209 cases proved fatal. There was a predominance of males (72%) and of deliberate intent (85%) involved in the fatalities (Table 3). The mean age for males was 44.6 (S.D. = 16.5) and 54.1 for females (S.D. = 14.2).

71% of fatalities involved concentrated liquid formulations (Table 3) and 22% granular formulations. There was a marked predominance of male fatalities involving the liquid formulations (78% male, 22% female) although there was no such difference with the granular products (54% male, 46% female).

Table 3 Type of product, intent and sex of patient involved in 209 fatalities reported to the NPIS (1980–1985)

	Accidental	Deliberate	NK
Liquid concentrate			
Male	4	100	12
Female	—	30	2
Total = 148			
Granular			
Male	3	21	1
Female	2	18	1
Total = 46			
NK			
Male	—	8	2
Female	1	1	3
Total = 15			
Totals: 209	10	178	21

Note: Liquid concentrate: Gramoxone, Dextrone, Gramonal, Cleensweep
Granular: Weedol, Pathclear

Of the 209 fatalities, 204 were due to ingestion of the product, two were due to injection, one intravenously and one intramuscularly and in three cases the route of exposure was not known.

Information was available as to the geographical distribution of 173 of the fatal cases. In absolute numbers most fatalities occurred in Greater London,

West Midlands and Belfast. However, this could be due to the large populations and/or the presence of centres taking an interest in the treatment of paraquat poisoning. Figure 4 shows that, when corrected for population differences, there are disproportionately large numbers of fatalities (seven or more per million) occurring in Belfast, Devon, Cornwall, Norfolk, West Sussex and West Glamorgan—a pattern which probably reflects the scale of the agricultural industry in these areas.

Information regarding occupation was only available for 67 of the 209 fatalities. Of these 39% had occupations which gave ready access to concentrated paraquat products, the remaining occupations were varied, with no obvious relationship to agriculture.

There are differences between the number of fatalities reported to the NPIS and those recorded from death certificates in England, Wales and Scotland. Both sources of data contain an unknown degree of bias. The NPIS relies principally on voluntary reporting of cases, although since 1980 by following up cases reported to the manufacturer or in newspapers the surveillance has been more complete. Official mortality statistics rely on the correct diagnosis of the cause of death which has been shown to be inaccurate in many instances of poisoning (Vale, Buckley & Meredith, 1984). If the number of deaths reported to the NPIS are compared to those reported by the OPCS and Registrar General of Scotland, the differences are small, e.g. 41 compared with 40 in 1982, 33 compared with 41 in 1983 and 32 compared with 30 in 1984. The degree of overlap remains unknown, requiring comparison of death certificates with NPIS records, and has not been possible within the scope of this study. In Eire, mortality statistics over the period 1967–1976 were obtained from a study combining official mortality and PCC statistics (Fitzgerald *et al.*, 1978), whilst after 1976, statistics were obtained solely from the PCC. There does not seem to be any great jump in the mortality trend shown in Figure 1 so perhaps differences between PCC and official mortality statistics are in fact small.

b. Other countries Mortality data from a survey into the incidence of paraquat poisoning amongst members of the EAPCC is shown in Table 4 together with information from other PCC's and literature. There are wide differences from country to country in the annual numbers of deaths due to paraquat per year, ranging from 1300 in Japan to 1 in Denmark and zero in Sweden. There are also wide variations in the number of fatalities per million population, e.g. 0.004 per million (USA) and 47.0 per million (Fiji). The mortality ratios range from 74% in one French study (Frelon *et al.*, 1983), 58% (Fiji) and 52% (Poland) to 0.6% (USA) suggesting that the proportion of suicides and accidental exposures are different in

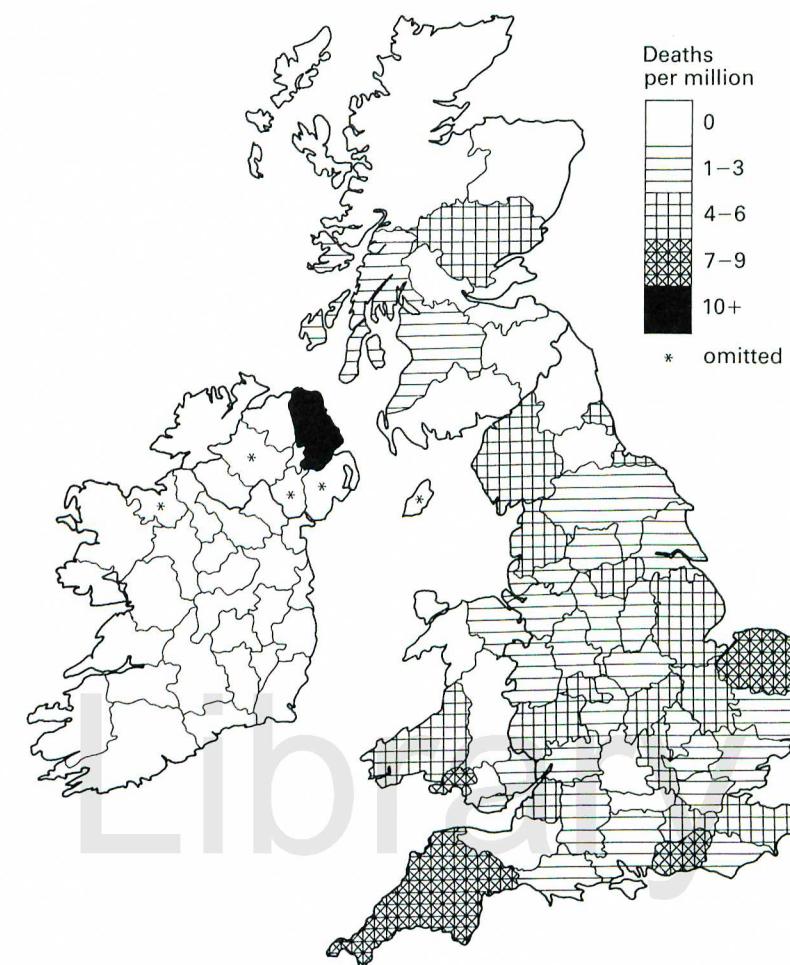


Figure 4 Deaths due to paraquat 1980–1985 (UK): Deaths per million population by county as reported to NPIS. (*n* = 173.)

different countries. Although the figures are not strictly compatible due to uncertainties with the populations covered, they do indicate that some countries have bigger problems with paraquat poisoning than others.

In France, paraquat poisoning has been monitored in detail by Poison Control Centres (Conso, 1979; Frelon, Merigot, Garnier *et al.*, 1983; Ethymiou, 1983). Paraquat was first marketed there in 1965, but fatalities were not recorded until 1973, rather later than in the UK. Accidental deaths declined in proportion to suicides over the period 1973 to 1977. All deaths resulted from ingestion. Ethymiou (1983) reported that although accidental and occupational poisoning represented 74% of all cases, suicidal poisoning was associated with the highest mortality, as were the more concentrated products. Over a

three-year period only one child died. More cases were reported in rural areas. Hence the situation in France is very similar to the UK.

A series of reviews concerning poisoning cases in Malaysia (Amarasingham & Lee, 1969; Amarasingham & Hee, 1976 and Amarasingham & See unpublished data) found that paraquat has replaced arsenite as the most commonly consumed poison. From 1977 to 1981 paraquat was responsible for 31% of all poisoning cases, with 79% mortality. The incidence of males and females was similar and poisoning was predominantly due to its suicidal use by the poorer ethnic groups who presumably had greater access to the product. Accidental cases of poisoning occurred after the concentrated formulations were decanted locally into poorly labelled containers.

Table 4 Fatalities due to paraquat reported internationally (over the years 1980–1984)

Country	Population (millions)	Deaths per annum (average)	Deaths per million population per annum	Cases per million population per annum	Mortality % (average)	Source
UK	56.6	37.6	0.66	3.3	20	NPIS
England & Wales	49.6	30.3	0.61	—	—	OPCS
Scotland	5.2	8.2	1.6	—	—	Registrar General
Denmark	5.1	1.0	0.20	—	—	Copenhagen PCC
France	54.2	—	—	1.7	—	Wickstrøm*
		20.0	(0.36)	(0.5)	74	Frelan 1983
Germany (West)	61.6	1.3	0.02	—	—	Wickstrøm*
Greece	9.8	—	—	6.2	—	Athens
Eire	3.5	9.4	2.7	15.8	18	Dublin PCC
Netherlands	14.3	—	—	2.0	—	Wickstrøm*
Czechoslovakia	15.4	2.5	0.16	—	—	Wickstrøm*
Norway	4.1	0.25	0.06	—	—	Wickstrøm*
Poland	36.7	4.3	0.12	0.23	52	Wickstrøm*
Spain	37.9	—	—	0.9	—	Wickstrøm*
Sweden	8.3	—	—	0.07	—	Stockholm PCC
Switzerland	6.5	1.8	0.28	1.3	21	Wickstrøm*
Israel	4.1	1.5	0.37	—	—	Haifa PCC
Australia	15.4	—	—	0.6	—	Canberra PCC
Fiji	0.67	31.5	47.0	80.6	58	Groundar 1984
Japan	118.4	1300	11.0	—	—	Naito 1986
USA	232.0	1.0	0.004	0.7	0.6	AAPCC

* = Wickstrøm, E. personal communication

Population sources: Eurostat 'Basic Statistics of the Community' 1984
UK CSO 'Regional Trends' 1985

Prevention

A range of measures have been introduced or proposed for the prevention of paraquat poisoning.

1. Communication

Information concerning the toxicity of paraquat, correct usage and the dangers of inappropriate storage should be given to agricultural and domestic users. Product labelling is one way of communicating this information. The earliest product labels for paraquat gave no indication of its toxicity, but when the problem of poisoning became apparent appropriate changes were made and present day labels leave the user in no doubt about the need to handle the product with care. Labelling should be in an appropriate language with symbols carefully chosen to be meaningful to the user. For example in some parts of the world the snake is more meaningful as a hazard warning of poison than the skull and crossbones.

No matter how good the label, it cannot be assumed that the user will read it carefully. It is therefore important to use additional forms of communication; posters and booklets such as those produced by

GIFAP (GIFAP 1983), appropriate audio visual aids and educational campaigns by the press and television regarding safe handling and storage. Media coverage of paraquat poisoning can have a detrimental effect reports of individual cases, often sensationalised may influence others to use paraquat as a means of suicide (Barracough, Shephard & Jennings, 1977). Therefore restricting or controlling such publicity might help reduce the number of suicides using paraquat (Hayes, 1980).

2. Packaging

Restricting pack size is an obvious way to limit the dose likely to be ingested. Additionally the type of package can affect the accessibility of the product. The proposed Child Resistant Packaging Regulation will not require child resistant closures for paraquat containing products currently on sale in the UK since they will not apply to solids or products exclusively for use in agriculture [Child Resistant Packaging Regulations 1986 (Draft)]. It is unlikely that the would affect the incidence of serious poisoning in children since children do not ingest toxic amounts of

the domestic products or gain access to the commercial preparations in their original containers. Accidental poisoning with these products in adults and children normally occurs as a result of inappropriate decanting and labelling. Packaging changes are unlikely to deter the suicidal patient.

3. Formulation changes

Changes in the concentration of paraquat within a product will also limit the dose ingested. Thus the marketing of a 2.5% w/w granular formulation represents a reduction in hazard from the earlier 5% w/w formulation. It has been shown that the granular formulation is less of a hazard than the liquid concentration (Table 3) and it has been proposed in this respect that a diluted liquid concentrate, 10% w/v, should replace the 20% w/v product currently marketed.

Other formulation changes have involved the use of 'additives'. An unpleasant smelling 'stenching' agent was added to liquid formulations in 1975 and in 1981 a blue colour was added to liquid and solid paraquat products to serve as a warning.

In 1977 a centrally-acting emetic agent, codenamed PP796, was added to liquid formulations at a concentration of 0.05% w/v and to solid formulations at a concentration of 0.02% w/w. This concentration of emetic was calculated to cause vomiting if the minimum lethal dose was swallowed and in animal experiments such a concentration increased the lethal dose of paraquat by a factor of three to five (Rose, 1976). Recently (1985) the concentration of emetic in solid formulations has been doubled. Two authors have commented on the effectiveness of the emetic in reducing mortality in man. In France it was concluded that the emetic (identified in 14 cases, 11 of whom died) did not modify prognosis. In contrast preliminary findings of a study in the UK have found that there may be some reduction in mortality with emetic addition (A. P. Whitehead, personal communication). Emetic addition was not associated with any adverse effects (Denduys-Whitehead, Hart & Volans, 1985). Even so the efficacy of the emetic at reducing mortality in man remains to be substantiated.

Another suggestion for prevention has been put forward as a result of the development of a novel formulation which forms a semi-solid mixture when small amounts of water are added, thus making it difficult to ingest large quantities (Naito & Yamashita, 1986).

4. Legislation

Legislation has restricted the availability of the commercial concentrate in many countries and in some countries a total ban has been applied (West Germany and Sweden). In the UK the Poisons Act of 1972 restricts the sale of concentrated formulations to

'persons engaged in the trade or business of agriculture, horticulture or forestry'. The sale of these concentrated products is further restricted by limiting the number of licensed dealers. In Eire, similar legislation was passed in 1968 and 1975. The effects of this legislation on the incidence of paraquat poisoning were studied by Fitzgerald *et al.* (1978) who found that there was a drop in the number of accidental poisonings, due to a decrease in the practice of decanting commercial products into household containers. There was no change in the number of suicides after this legislation was passed. Legislation may have the effect of increasing other forms of suicidal poisoning. It was following a ban of arsenite as a weedkiller in Malaysia in 1976 that paraquat poisoning became such a problem (Amarasingham & See, unpublished data). Those countries where paraquat is banned can be seen from Table 2 to have a very low incidence of paraquat poisoning. However such a severe course of action may not be appropriate for all countries and must take into account the agricultural importance of paraquat in that country.

Asked whether measures taken against paraquat poisoning had been effective, members of the European Association of Poison Control Centres (EAPCC) concluded that the addition of an emetic or staining agent had not had the desired effect and that strict regulations on the sale of the liquid concentrate did not seem to be wholly effective (Wickstrøm, personal communication).

Discussion

Comparisons of the incidence and severity of paraquat poisoning between different countries are severely limited by the lack of standardised methods of official data collection and recording. Nevertheless it is apparent that paraquat remains an important cause of mortality worldwide and there is little evidence that paraquat poisoning is decreasing in frequency.

There are differences in the incidence of paraquat poisoning amongst the countries studied. There are also regional differences within the UK, Northern Ireland and Scotland have higher incidences than England and Wales, and paraquat poisoning in Eire has always had a higher incidence than in the UK. In some countries paraquat has not so far presented a serious problem in spite of its widespread usage—for example, USA and Australia. In contrast Japan and a number of other countries, notably Fiji, are currently facing epidemics of paraquat poisoning far more severe than those seen in Europe.

Mortality from paraquat poisoning is closely related to suicidal intent; thus in the USA (mortality 0.6%) 88% of cases were accidental whilst in Fiji (mortality 58%), 66% had suicidal intent. Additionally the predominance of males amongst fatalities correlates well

with the known epidemiology of suicides (Weissman, 1974). \rightarrow suicidal use of paraquat in the UK

The increase in suicidal use of paraquat in the UK over the period 1966–1975, accounts for the rise in fatalities (Figure 3). Why there should have been this increase in so many countries is unknown. In the UK there was no proportionate increase in sales of the commercial product over the period when the rapid increase in fatalities occurred (T. B. Hart, personal communication). However the availability of the liquid concentrate remains an important factor. The wide range of occupations recorded amongst fatalities may mean that legislation restricting the availability of paraquat is not sufficient. Substitution and public awareness are additional factors which may influence the use of a particular product for suicide (Low *et al.*, 1981). Substitution has been shown to have had an effect in Malaysia where paraquat replaced arsenite poisoning but the influence of substitution in the UK is not known. Public awareness, increased by media reporting may be an important factor but remains difficult to investigate.

In many countries serious accidental and occupational poisoning and poisoning in children is rare. The nature of paraquat poisoning is largely suicidal and it is unlikely that current preventative measures

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In many countries serious accidental and occupational poisoning and poisoning in children is rare. The nature of paraquat poisoning is largely suicidal and it is unlikely that current preventative measures

will influence the number of deaths occurring each year. Few preventative measures have been monitored in such a way as to demonstrate their effectiveness.

On the basis of our experience in the UK, we believe that Poison Control Centres (PCCs) have an important role in monitoring the incidence and severity of poisoning and providing epidemiological data. PCCs are well placed then to develop schemes to evaluate preventative measures. Care must be taken when making direct comparisons between different PCCs because of the different populations covered and differences in the methods used to assess cases. There is currently much interest in the suggestion that PCCs should agree to standardise some aspects of data collection. We would tentatively suggest that since paraquat poisoning in Europe is widespread and involves relatively small numbers of a discrete type of poisoning it would form a useful model for international collaboration between PCCs.

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